Efficacy of larotrectinib in adolescents and young adults with TRK fusion cancer

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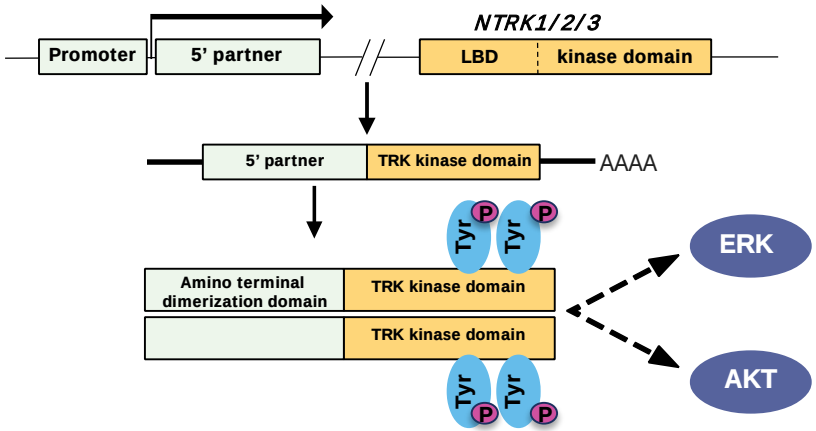
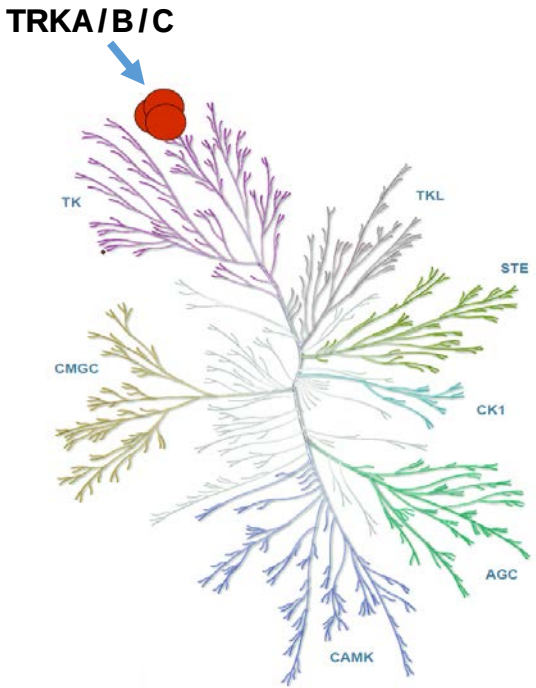
Larotrectinib is a selective, CNS-active TRK inhibitor

NTRK gene fusions are rare but recurrent oncogenic drivers





- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC_{50} in cellular assays)
- Demonstrated activity in CNS disease[1]
- Liquid formulation allows dosing of children as young as at birth and delivers equivalent pharmacokinetics to capsules

CNS, central nervous system

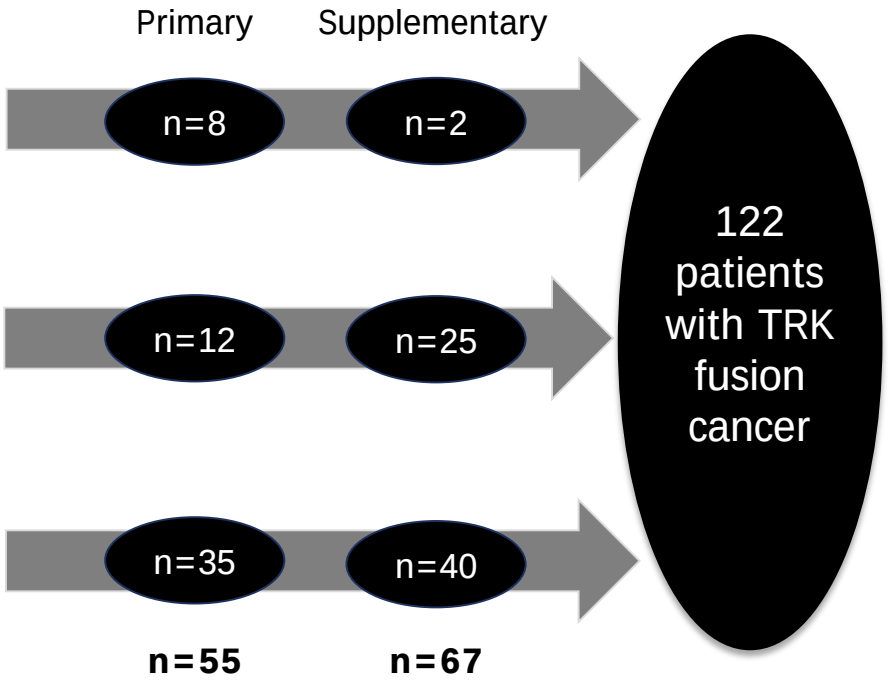
[1]Ziegler et al. *Br J Cancer*. 2018; 119:693–696

Patients with TRK fusion cancer: Integrated dataset

Adult phase I
- Age ≥18 years
- Advanced solid tumors

SCOUT: pediatric phase I/II
- Age ≤21 years
- Advanced solid tumors

NAVIGATE: adult/adolescent phase II 'basket' trial
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer



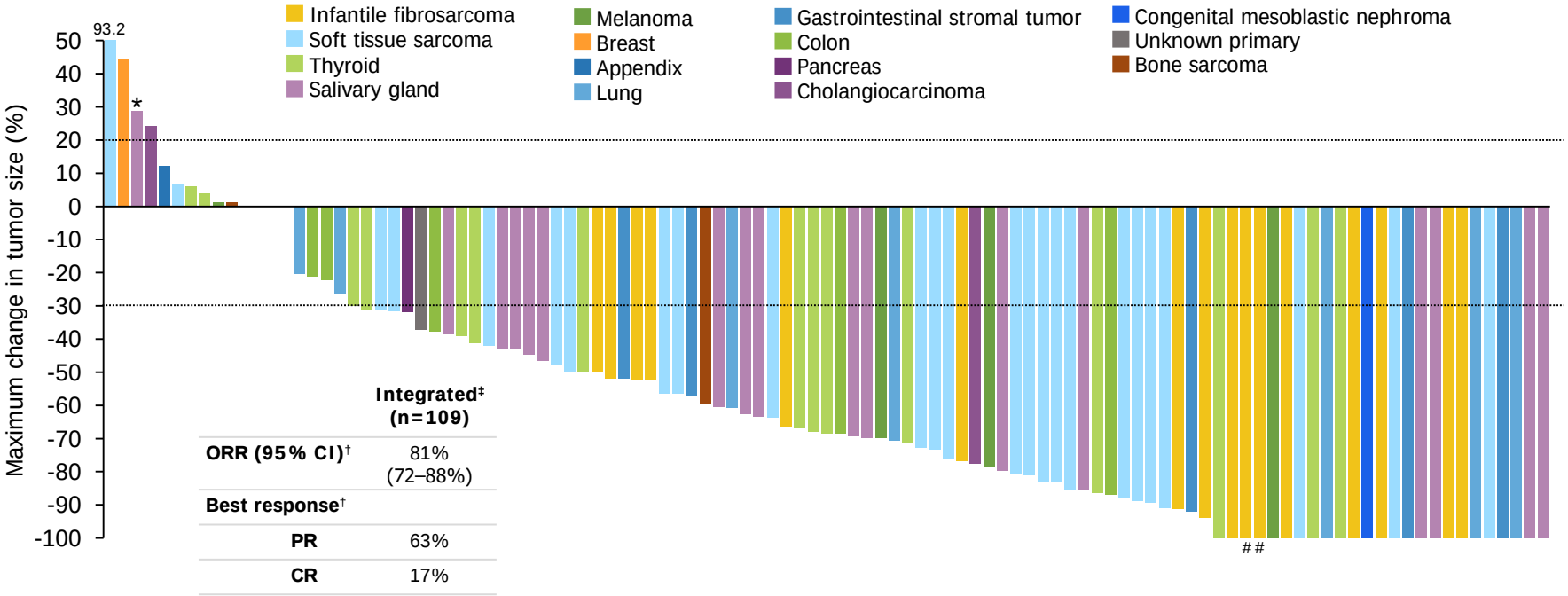
- ***NTRK* gene fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cutoff: 30 July 2018

BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors

Lassen et al. presented at ESMO 2018; Ann Oncol. 2018; 29:(suppl_8 abstr 409O)

Integrated dataset: Larotrectinib is efficacious regardless of tumor type

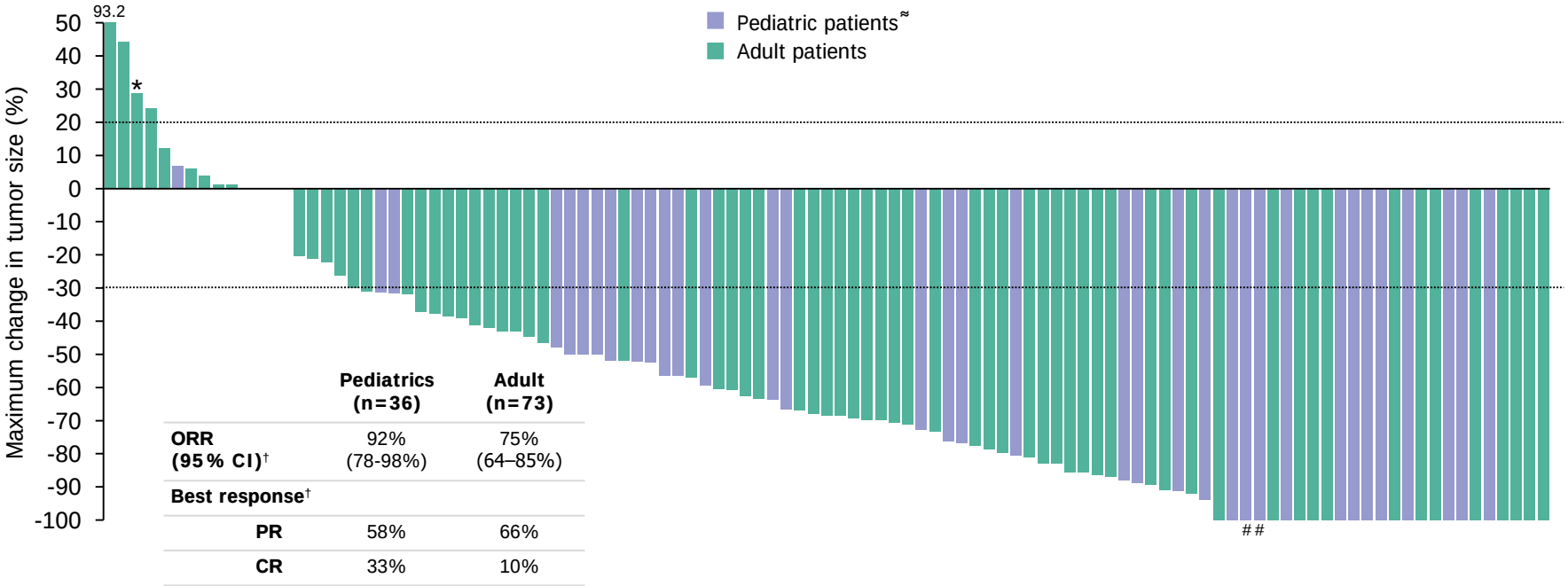


	Integrated‡ (n=109)
ORR (95% CI)†	81% (72–88%)
Best response†	
PR	63%
CR	17%

‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment *Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1. Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.
CR, complete response; ORR, objective response rate; PR, partial response
Lassen et al. presented at ESMO 2018

Investigator response assessments, as of 30 July 2018

Integrated dataset: Larotrectinib is efficacious regardless of age



	Pediatrics (n=36)	Adult (n=73)
ORR (95% CI)†	92% (78-98%)	75% (64–85%)
Best response†		
PR	58%	66%
CR	33%	10%

Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment. ≈Age <21 years *Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1. Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.
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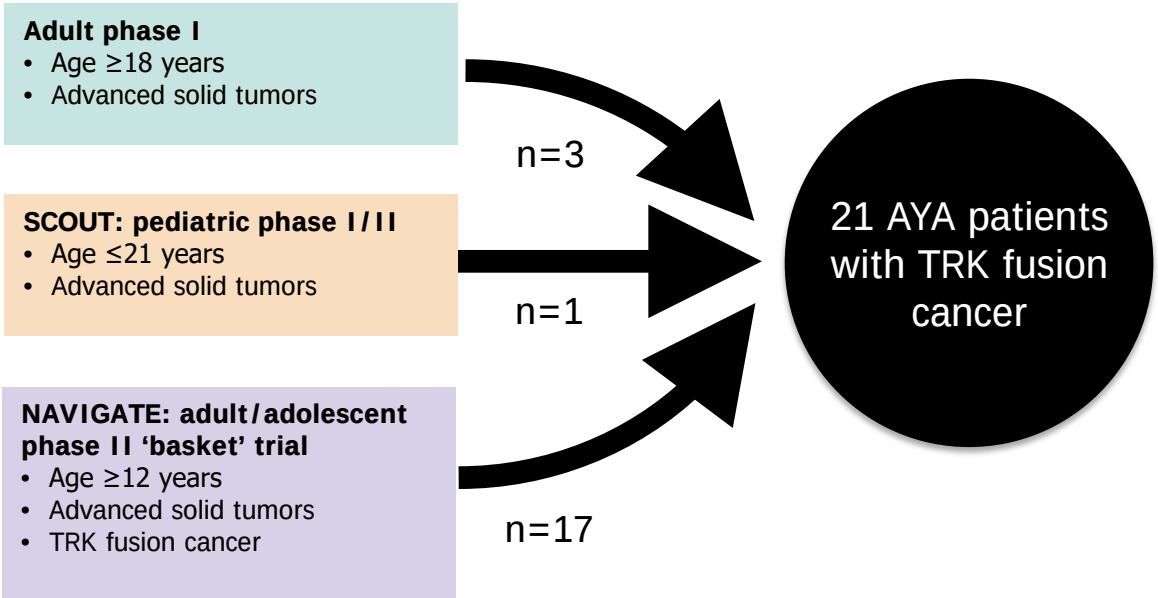
AYA patients with TRK fusion cancer



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Data cutoff: 30 July 2018

AYA, adolescent & young adult

Baseline characteristics

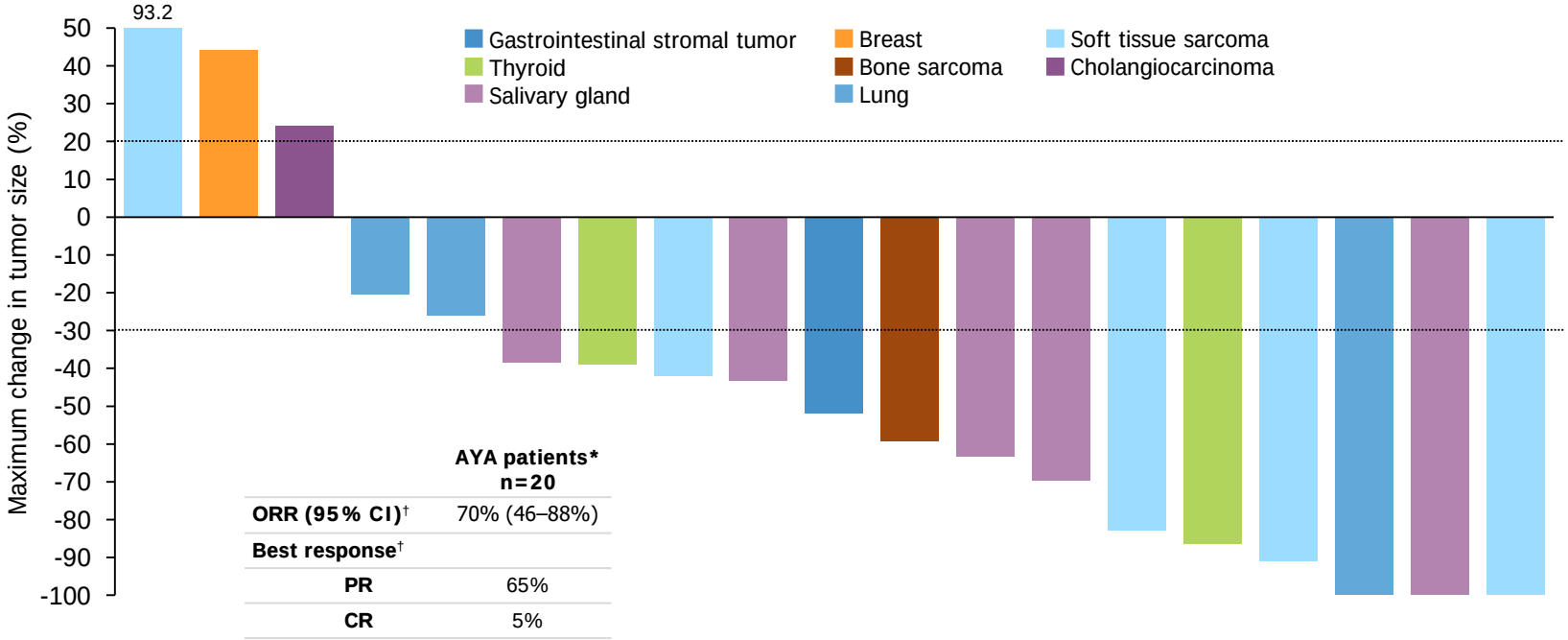
Characteristic	n=21
Gender, n (%)	
Male	11 (52)
Female	10 (48)
Median age (range), years	31 (20–39)
Age group, n (%)	
15–<21 years	1 (5)
21–30 years	8 (38)
31–39 years	12 (57)
Tumor type, n (%)	
Salivary gland	5 (24)
Soft tissue sarcoma	5 (24)
Lung	3 (14)
Thyroid	3 (14)
Breast	1 (5)
Bone sarcoma	1 (5)
Cholangiocarcinoma	1 (5)
Gastrointestinal stromal tumor	1 (5)
Melanoma	1 (5)

Baseline characteristics

Characteristic	n=21
***NTRK* gene fusion**, n (%)	
NTRK1	9 (43)
NTRK2	0
NTRK3	12 (57)
ECOG PS, n (%)	
0	8 (38)
1	10 (48)
2	3 (14)
Disease status at study enrollment, n (%)	
Metastatic	19 (90)
Locally advanced	2 (10)
Prior cancer treatment, n (%)	21 (100)
Surgery	19 (90)
Systemic therapy	16 (76)
Radiotherapy	14 (67)
No. of prior systemic regimens, n (%)	
0	5 (24)
1	7 (33)
2	3 (14)
≥3	6 (29)

ECOG PS, Eastern Cooperative Oncology Group performance status

High response rate in AYA patients with TRK fusion cancer

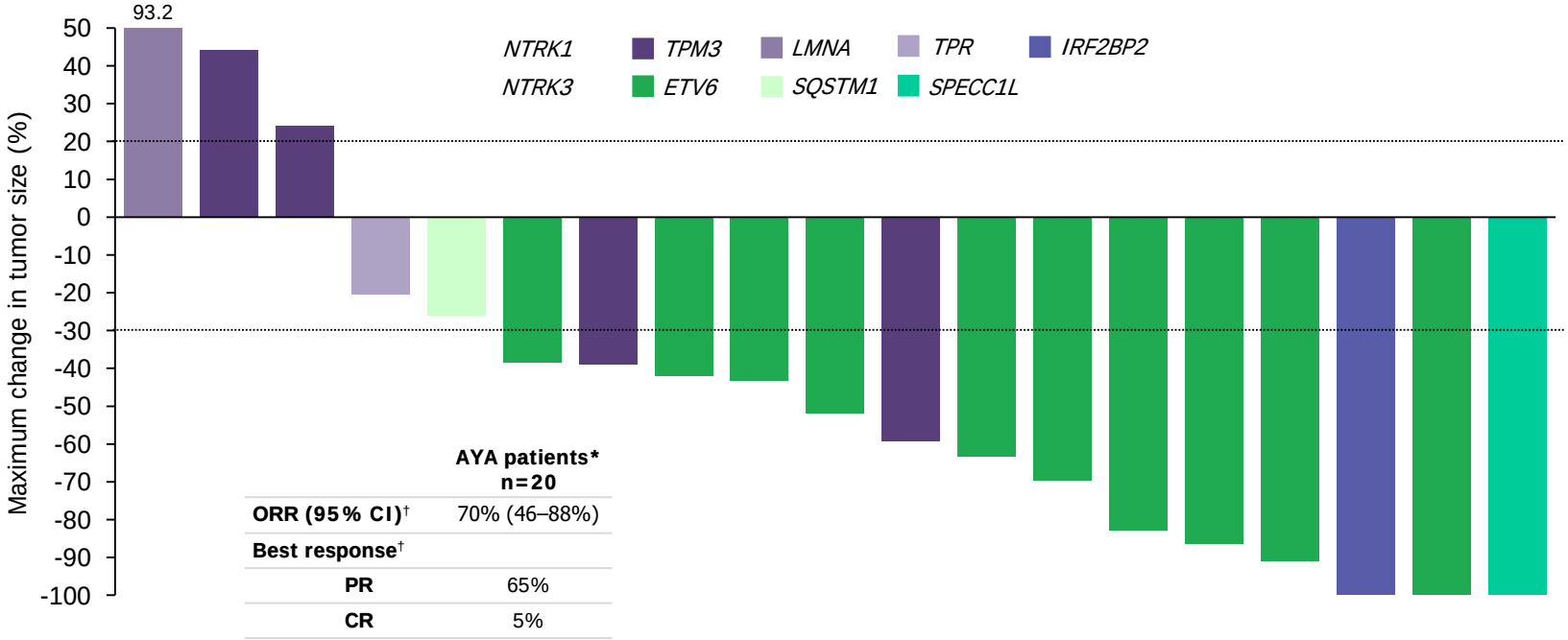


	AYA patients* n=20
ORR (95% CI)†	70% (46–88%)
Best response†	
PR	65%
CR	5%

*Evaluable patients; includes 1 unconfirmed PR pending confirmation; does not include 2 patients- 1 patient continuing on study and awaiting initial response assessment, and 1 patient discontinued treatment prior to any post-baseline tumor measurements; †RECIST 1.1.
CR, complete response; ORR, objective response rate; PR, partial response

Investigator response assessments, as of 30 July 2018

High response rate in AYA patients with TRK fusion cancer



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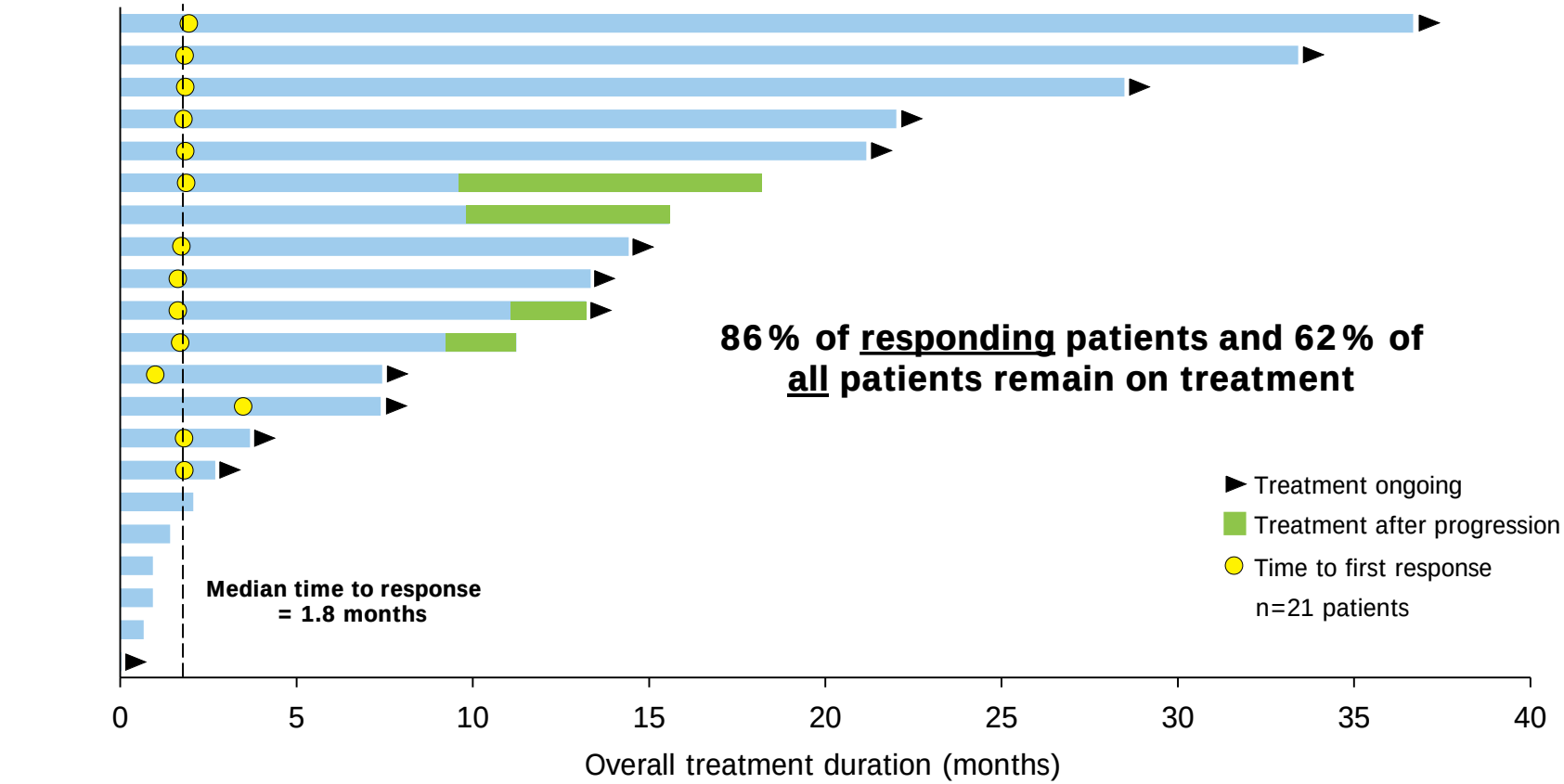
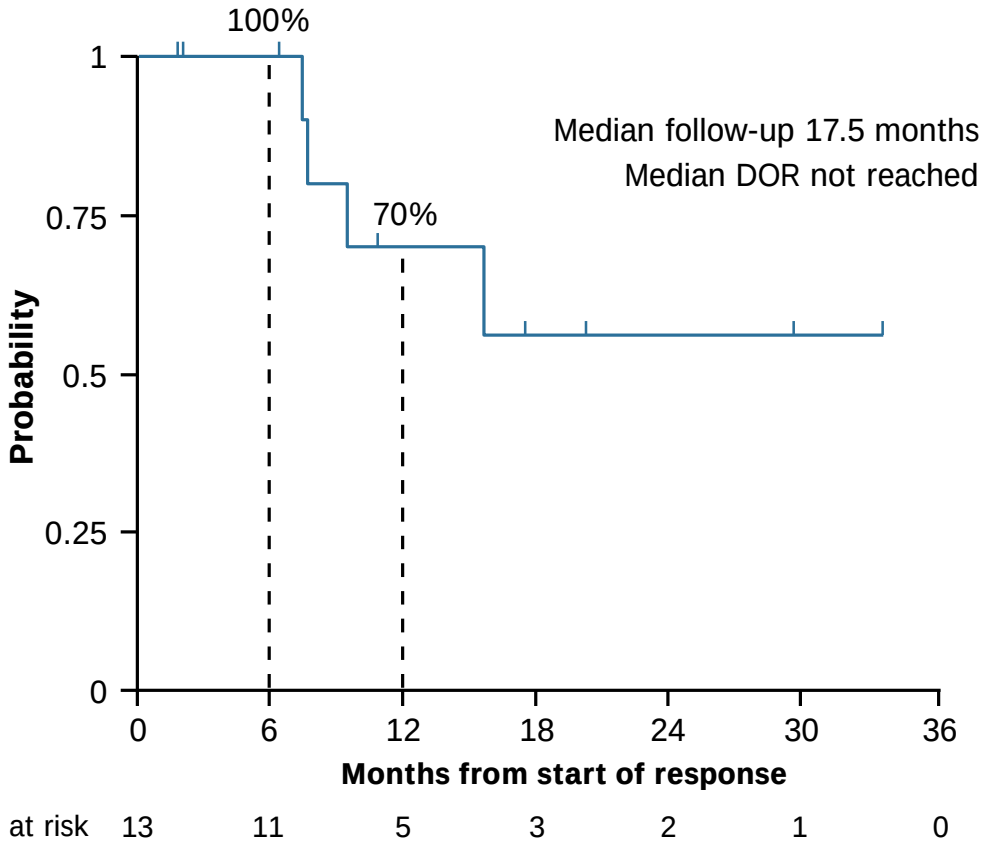
Duration of larotrectinib treatment



Investigator response assessments, as of 30 July 2018

Sustained responses with larotrectinib: Duration of response*



*In patients with confirmed complete or partial responses
DOR, duration of response

Investigator response assessments, as of 30 July 2018

Adverse events with larotrectinib: ≥15% in safety database (n=207)

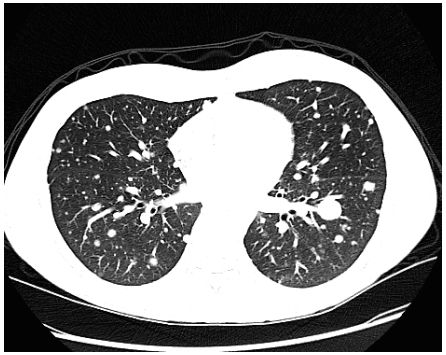
	Treatment-emergent AEs (%)					Treatment-related AEs (%)		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Fatigue	18	15	3	–	36	<1	–	18
Dizziness	25	3	1	–	29	<1	–	21
Nausea	24	3	1	–	29	1	–	15
Constipation	22	5	<1	–	27	–	–	12
Anemia	10	7	10	–	27	2	–	11
ALT increased	17	5	3	<1	26	2	<1	21
AST increased	18	5	3	–	26	1	–	19
Cough	23	3	<1	–	26	–	–	1
Diarrhea	16	6	1	–	23	–	–	5
Vomiting	17	6	<1	–	23	–	–	10
Pyrexia	12	5	<1	<1	18	–	–	1
Dyspnea	10	6	2	–	18	–	–	1
Headache	13	4	–	–	16	–	–	4
Myalgia	12	3	1	–	16	<1	–	7
Peripheral edema	12	4	–	–	15	–	–	7

- 11 (9%) of 122 patients with TRK fusion cancer required dose reductions – all maintained tumor regression on reduced dose
- 1 (<1%) of 122 patients with TRK fusion cancer discontinued larotrectinib due to an adverse event

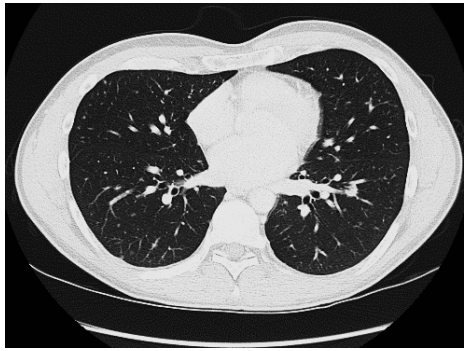
AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase

As of 30 July 2018

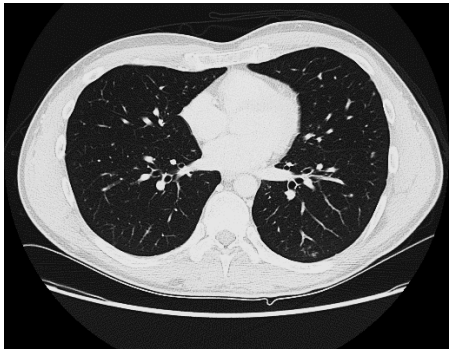
ETV6-NTRK3 fusion papillary thyroid cancer



Study baseline



Study cycle 3 day 1



Study cycle 7 day 1

- 33-year-old male with metastatic *ETV6-NTRK3* papillary thyroid cancer who had undergone multiple prior surgical resections, and received 2 prior lines of iodine therapy and trametinib/pazopanib
- Started on larotrectinib 100 mg BID
- Confirmed partial response by end of cycle 2 with 88% reduction in target lesion size per RECIST 1.1
- Continues on larotrectinib and in response, with duration of treatment 33.4+ months as of July 2018

Conclusions

- Larotrectinib yields a high response rate in AYA patients with TRK fusion cancer, regardless of tumor and fusion type:
  - ORR of 70% (n=21) per investigator assessment

- At a median follow-up of 17.5 months in the AYA dataset:
  - Median DOR not reached
  - An estimated 70% of responses were ongoing at 12 months

- Prolonged therapy with larotrectinib appears to be associated with manageable toxicity

- FDA approved first ever TRK inhibitor (Nov 26 2018); MAA submitted to EMA in August 2018

- Genomic profiling with assays capable of identifying *NTRK* gene fusions should be strongly considered in AYA patients with solid tumors of all histologies when determining systemic treatment options

Acknowledgments

- We thank the patients and their families, many of whom traveled long distances to participate in these studies
- These studies are funded by Loxo Oncology, Inc and Bayer AG

SCOUT

NAVIGATE